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Review

Regulation of gene transcription by mitogen-activated protein kinase signaling pathways

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Abstract

Mitogen-activated protein kinase (MAPK) signaling pathways are key mediators of eukaryotic transcriptional responses to extracellular signals. These pathways control gene expression in a number of ways including the phosphorylation and regulation of transcription factors, co-regulatory proteins and chromatin proteins. MAPK pathways therefore target multiple components of transcriptional complexes at gene promoters and can regulate DNA binding, protein stability, cellular localization, transactivation or repression, and nucleosome structure. Recent work has uncovered further complexities in the mechanisms by which MAPKs control gene expression including their roles as integral components of transcription factor complexes and their interplay with other post-translational modification pathways. In this review I discuss these advances with particular focus on how MAPK signals are integrated by transcription factor complexes to provide specific transcriptional responses and how this relates to cellular function.
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Keywords: Gene expression; Signal transduction; Transcription factor; Chromatin; MAP kinase; Phosphorylation

1. Introduction

The exposure of cells to extracellular signals elicits changes in gene expression that promote appropriate physiological responses. These signals activate multiple intracellular signaling pathways that are integrated at gene promoters and target transcription factors, co-regulators and chromatin proteins. The phosphorylation and de-phosphorylation of transcriptional regulators mediated by specific protein kinases and protein phosphatases is the most common mechanism of controlling gene expression [1,2]. The MAPK group of signaling pathways are important mediators of transcriptional responses to extracellular signals that include growth factors, hormones, cytokines and environmental stresses [3–10]. These pathways are evolutionarily conserved amongst eukaryotes and in recent years a large number of proteins involved in gene transcription have been identified as their targets [8]. MAPK pathways can alter the activities of transcriptional regulators in many ways including controlling their localization in cells, their expression and stability, their ability to bind to other components of transcriptional complexes and to DNA, and their ability to remodel chromatin structure. Many of these mechanisms have been discussed extensively in previous reviews [1,8–10]. In this review I focus on recent advances including (i) how transcription factors can interpret the kinetics of MAPK activity and therefore respond appropriately, (ii) how components of MAPK pathways, in addition to their enzymatic role, are integral parts of transcriptional complexes, and (iii) how MAPK pathways and other post-translational modification pathways are integrated to control gene expression.

2. MAPK signaling pathways

MAPK signaling pathways are evolutionarily conserved in eukaryotes and are involved in many cellular processes including growth, differentiation, apoptosis and the immune response [3–7]. These pathways feature a conserved signaling cascade downstream of small GTPases of the Ras and Rho families. The cascade consists of a MAPK kinase kinase (MKKK) which phosphorylates and activates a MAPK kinase

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(MKK) which then activates the MAPK by phosphorylation on Thr and Tyr residues within a conserved motif located in the activation loop of the kinase [3–7].

In the budding yeast *Saccharomyces cerevisiae* there are five MAPK pathways which control diverse cellular processes including mating, sporulation, cell wall integrity, invasive growth and pseudohyphal growth, and the response to high osmolarity [3]. For example, in response to high osmolarity, the high osmolarity glycerol-1 (Hog1) pathway is activated leading to increased expression of enzymes required for the synthesis of the osmotic stabilizer glycerol, while genes required for mating are controlled by a pathway that signals via the Fus3 and Kss1 MAPKs [3].

In mammalian cells there are four major MAPK pathways leading to the activation of extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38, and extracellular signal-regulated kinase 5 (ERK5; also called Big MAP kinase-1 (BMK1)) [4–7]. There is increased complexity within the mammalian pathways due to the occurrence of multiple gene products (i.e. ERK1 and ERK2; JNK1, JNK2, and JNK3; p38α, p38β, p38γ, and p38δ) [4–6]. In addition, further isoforms are generated by differential splicing. For example the three *Jnk* genes encode a total of ten distinct isoforms [11]. The ERK pathway is mainly activated by growth factors and hormones while the JNK and p38 pathways are activated by environmental stress and pro-inflammatory cytokines [4–6]. The ERK5 pathway is activated by specific mitogens and stresses [7]. In addition to the four major mammalian MAPK pathways there are a number of other protein kinases that share significant sequence homology to MAPKs [12,13]. Although relatively poorly characterized, a number of these, including ERK7, ERK8 and Nemo-like kinase (NLK), have also been shown to regulate transcriptional events [12,13]. The components of MAPK pathways associate with many types of regulatory proteins including protein phosphatases, which de-phosphorylate and inactivate the protein kinase components of the pathway [14], and scaffold proteins which co-localize components of the pathways, regulate their activities, and direct the pathways to specific targets [15,16].

The minimal consensus phosphorylation motif in MAPK substrates is [Ser/Thr]-Pro [8–10]. Activated MAPKs can directly phosphorylate their substrates in the cytoplasm or nucleus to regulate transcription [8–10]. MAPKs also phosphorylate and activate downstream protein kinases that can target proteins involved in transcription [17]. For example, mammalian MAPKs activate members of the Ribosomal S6 kinase (RSK), MAPK-interacting kinase (MNK), MAPK-activated protein kinase (MAPKAPK), and the mitogen- and stress-activated protein kinase (MSK) families [17].

The organization and regulation of mammalian MAPK pathways is highly conserved between yeast and mammals [3–7]. Indeed, complementation experiments have demonstrated that some mammalian MAPKs can functionally replace their homologs in yeast [18]. It is likely therefore that the mechanisms governing MAPK regulation of transcription are similar across eukaryotes.

3. Interaction of MAPKs with transcription factor complexes

MAPKs can bind to many types of proteins including substrates, other protein kinases, protein phosphatases, scaffold or adaptor proteins, cytoskeletal proteins, as well as transcriptional proteins [19,20]. In order to efficiently phosphorylate their substrates, including transcription factors, MAPKs often directly interact with them via conserved docking sites [19,20]. In some instances such docking sites on transcription factors can act as sensors that detect the strength and duration of MAPK activity in cells [21], while other recent work suggests that MAPKs could, in addition to their enzymatic role, play important adaptor roles themselves and directly recruit proteins into transcription factor complexes on gene promoters [22].

3.1. Docking of MAPKs to their substrates

In addition to the [Ser/Thr]-Pro phosphoacceptor motif, MAPK substrates contain docking sites for binding to the MAPK [8,19,20]. These docking sites are essential for efficient phosphorylation to occur and also impart specificity as they selectively bind to MAPK sub-types [8,19,20]. Several types of docking sites have been uncovered, the best characterized of which are the D (or δ)-domains which feature a cluster of basic residues upstream of a Leu-x-Leu motif and/or a hydrophobic triplet [8,19,20]. D-domains can be found upstream or downstream of the phosphoacceptor sites and the exact composition and spacing of the residues determines the specificity for particular MAPKs [8,19,20]. In addition, X-ray crystallography experiments featuring D-domain peptides bound to MAPKs indicate that D-domains induce distinct conformation changes in different MAPKs that may also contribute to the specificity of phosphorylation [23–25]. D-domains have been demonstrated to play an extensive role in MAPK signaling in both yeast and mammals, as they are also present in other MAPK binding proteins including scaffold proteins, MKKs, and protein phosphatases [19,20]. A second type of docking site commonly found in transcription factors is the DEF domain (docking site for ERK, FXFP; also known as the FxFP motif) that can be recognised by ERK and the p38α isoform and is usually found downstream of the phosphoacceptor sites [8,19,20,26,27]. This motif contains a consensus sequence of [Phe/Tyr]-x-[Phe/Tyr]-Pro. MAPKs can also bind to other sites in substrates that do not resemble D-domains or DEF domains, suggesting that there may be variety of MAPK docking interactions with their substrates [28,29].

It is important to note that some substrates contain more than one type of docking site and can recruit combinations of MAPKs depending on the stimuli. For example, JunD contains both a D-domain and a DEF domain [30]. The D-domain is required for binding to JNK and for JNK-mediated phosphorylation of JunD in response to stress, while both the D-domain and the DEF domain contribute to ERK phosphorylation of JunD in response to growth factors [30]. Further complexity arises from the observation that the related AP-1 family member c-Jun (which

contains a D-domain but not a DEF domain) binds to JNK via its D-domain and can heterodimerize with JunD [31]. This allows the c-Jun-bound JNK to phosphorylate JunD in *trans* [31]. As JunD is less efficiently activated by JNK compared to c-Jun [30,31], it is possible that at promoters containing c-Jun/JunD heterodimers the c-Jun-bound JNK contributes to a more robust activation of JunD transcriptional activity. Like JunD, the ETS-domain factor Elk-1 recruits ERK to both D and DEF domains and it has been reported that each domain can target ERK to phosphorylate specific residues within the Elk-1 transcriptional activation domain (TAD), thereby collaborating in Elk-1 activation [32]. In contrast, distinct MAPK docking sites may direct phosphorylation events that have opposing effects on transcription factor function, as exemplified by a related ETS-domain factor Net/SAP-2, which binds to ERK and JNK via two separate D-domains [33]. These examples suggest that transcription factors utilize different combinations of MAPK docking sites to direct phosphorylation events that regulate their activities in response to distinct stimuli.

Due to their central roles in many pathological conditions there have been tremendous efforts to generate specific pharmacological inhibitors of MAPK pathways [34]. In the future, exploiting the specificity of docking domains for MAPKs may prove a viable alternative to the generation of ATP-competitive inhibitors that inhibit protein kinase activity [35]. The ATP binding region displays a high level of conservation amongst the MAPK family groups and also with other protein kinases which has made the generation of highly specific inhibitors of MAPK activity problematic [34,35]. Recent work utilizing peptides derived from D-domains found that these could be potent inhibitors of MAPK signaling *in vivo*, while small molecule inhibitors of ERK binding to D-domains have been demonstrated to block ERK phosphorylation of substrates and to reduce the proliferation of cancer cell lines [29,35,36]. This raises the possibility that specific MAPK functions could be blocked *in vivo* through the targeting of distinct MAPK interactions. It is known that D-domains and DEF domains bind to distinct regions in ERK2 and that mutations in ERK2 that abrogate DEF domain binding do not block binding to D-domains or affect the ERK2 phosphotransferase activity [37,38]. In addition, peptides that are based on the D-domain can block ERK2 phosphorylation of Elk-1 but do not affect ERK2 phosphorylation of microphthalmia-associated transcription factor (MITF) which contains a different docking site [29]. Indeed, blocking MAPK docking sites may be an important mechanism for downregulating transcription factor function in cells. For example, the *Drosophila* transcriptional activator Pointed-P2 is activated following phosphorylation by dERK (Rolled) but this can be inhibited by the binding of Mae to the dERK docking site on Pointed-P2, which prevents dERK binding [39].

3.2. Docking sites on transcription factors can act as MAPK signal sensors

It has been known for some time that the duration and strength of MAPK signaling can regulate distinct cell fate decisions. For example, in PC12 pheochromocytoma cells the sustained activation of ERK leads to differentiation while transient ERK activation promotes proliferation [40]. Correlations between the duration of ERK signaling and cell behaviour have also been uncovered in other cell types. In fibroblasts sustained ERK activity is required for cell cycle re-entry and proliferation [21,40,41]. This occurs via the expression of proteins required for cell cycle re-entry such as cyclin D1 [21] and by the repression of anti-proliferative genes [41]. Recent studies have addressed the molecular mechanisms by which transcription factors interpret differences in ERK signaling kinetics and docking interactions appear to play a key role.

The immediate early gene (IEG) product c-Fos is a component of AP-1 transcription factor complexes and is expressed in response to growth factors that cause both transient and sustained ERK signaling [9,21,42]. However, the protein is unstable unless it is phosphorylated at the C-terminus. Under conditions where ERK activity is transient, the c-Fos protein is not phosphorylated and is degraded, while sustained ERK activity leads to C-terminal phosphorylation of c-Fos and its stabilization and activation [21,43] (Fig. 1A). The DEF domain of c-Fos plays a critical role in this process. c-Fos is initially phosphorylated at two C-terminal sites (Ser362 and Ser374) by ERK and the ERK-regulated protein kinase RSK [43] (Fig. 1A). In addition to stabilizing the c-Fos protein, these phosphorylations act as a priming event that permits the access of ERK to the DEF domain in c-Fos and leads to the phosphorylation of further sites (Thr325 and Thr331) which contribute to c-Fos transcriptional activity [43] (Fig. 1A). The importance of the DEF domain has been confirmed as the mutation of key residues disrupts c-Fos-mediated signaling [43].

In addition to c-Fos, a number of other DEF domain-containing IEG products can act as sensors of ERK activity including Fra-1, Fra-2, and c-Myc [44]. These IEG products appear to be highly sensitive as they can detect relatively small changes in ERK signal strength [44], however, they may also act as gatekeepers by only allowing efficient DEF domain-dependent phosphorylation of transcription factors when ERK activity reaches a threshold strength or duration. In addition, it is proposed that these transcription factors may contribute to sustaining nuclear ERK activation by retaining the active ERK in the nucleus via DEF domain binding and by preventing the interaction of ERK with MAPK phosphatases [21].

It is likely that transcription factors can sense the activity levels of other MAPKs in addition to ERK. For example, DEF domains have been demonstrated to bind to p38α in addition to ERK [27], while the duration of JNK activation by tumor necrosis factor (TNF) determines distinct cell fates [45].

A variation on this theme is the ability of docking sites in transcription factors to recognise the activation state of MAPKs. For example, experiments in fibroblasts have demonstrated that distinct JNK isoforms differentially regulate gene expression [46] and proliferation [47,48]. Fibroblasts that lack JNK1 activity have a small defect in proliferation while those deficient in JNK2 activity show enhanced proliferation [47,48]. This correlates with reduced levels of c-Jun and AP-1 activity in the

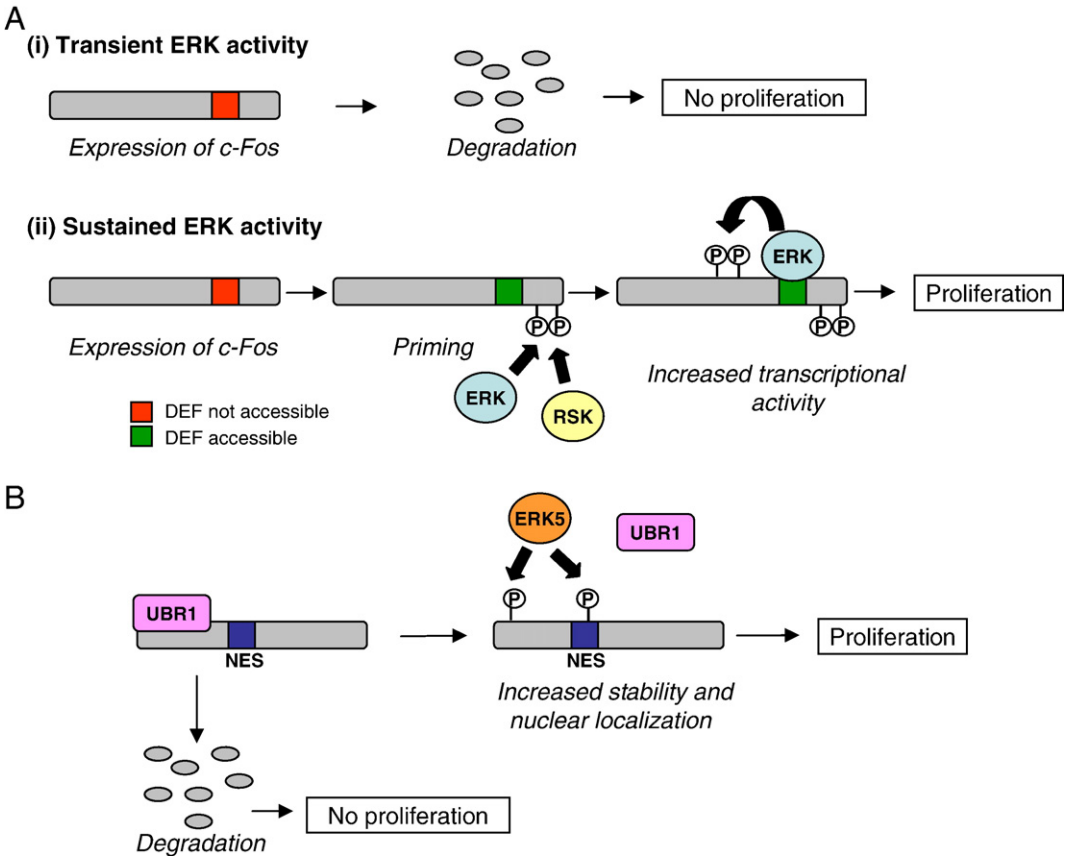

Fig. 1. MAPK regulation of c-Fos transcriptional activity and cell proliferation. (A) IEG gene products such as the AP-1 family member c-Fos can interpret the strength and duration of ERK MAPK activation in cells and direct distinct proliferative outcomes [21,43]. Stimuli that cause transient activation of ERK induce the expression of c-Fos but the protein is rapidly degraded by the proteosome. However, in response to sustained ERK activity, the expressed c-Fos protein is stabilized by the phosphorylation (P) of two sites within the C-terminus (Ser362 and Ser374) by ERK and RSK. This acts as a priming event that permits the DEF domain on c-Fos to bind to ERK which results in further phosphorylation of c-Fos (at Thr325 and Thr331) and subsequent transcriptional activation and cell proliferation [21,43]. (B) ERK5 regulates c-Fos stability and nuclear localization. ERK5 phosphorylates c-Fos at Ser32 and Thr232 (sites distinct from the ERK1/2 sites) and blocks c-Fos nuclear export as well as its binding to the E3 ubiquitin ligase UBR1, which can mediate c-Fos degradation [88,89]. Sustained ERK5 activity promotes c-Fos nuclear localization and stability resulting in enhanced cell growth.

JNK1-deficient cells and increased levels of both in the JNK2-deficient cells [48]. A model has been proposed whereby in unstimulated cells JNK2 preferentially associates with c-Jun via its D-domain resulting in the degradation of c-Jun by the ubiquitin-proteosome pathway [48,49], while in stimulated cells the specificity of c-Jun for JNK isoforms alters and it preferentially binds to activated JNK1 and is phosphorylated leading to its transcriptional activation [48]. However, it is also reported that the loss of JNK2 protein leads to enhanced JNK1 function indicating that the phenotype observed in JNK2-null fibroblasts may be a result of increased JNK1 activity, possibly due to reduced competition for upstream activators [50]. Indeed, using a chemical genetics approach to specifically inhibit JNK2 activity, rather than engineering the complete loss of JNK2 protein, it was demonstrated that both JNK1 and JNK2 positively contribute to c-Jun activity [50]. Binding studies of JNK isoforms to c-Jun [48,51], along with a study of ERK docking motifs in ETS2 [52], do, however, suggest that docking domains in transcription factors are capable of distinguishing between the activation states of highly similar MAPK isoforms, thereby contributing to signaling specificity.

3.3. MAPKs as components of transcription factor complexes

The well-documented interactions between MAPKs and transcription factors suggests that they may be part of transcriptional complexes at gene promoters. Indeed, studies have demonstrated that MAPKs can be retained in the nucleus by virtue of their interactions with transcription factors but until recently there was limited evidence supporting their recruitment to promoters. Now a number of studies, in particular those focussed on the high osmolarity sensing Hog1 pathway in *S. cerevisiae*, have provided strong evidence that MAPKs can be recruited to genes and are integral components of transcription factor complexes [22,53–55].

The Hog1 pathway coordinates an initial osmotic stress relief response of cells with the transcriptional up-regulation of genes required for adaptation to high osmolarity [56,57]. Hyperosmotic stress in the form of high salt concentration causes the rapid activation of Hog1 and also the dissociation of transcriptional regulators from chromatin [56,57]. Initially, Hog1 protects the ability of the cell to mount an appropriate transcriptional response by phosphorylating the Na+–H+ antiporter Nha1 and

the Tok1 potassium channel leading to Na+ efflux and re-association of transcriptional regulators with chromatin [57]. Active Hog1 can then regulate a number of transcription factors (e.g. Sko1, Hot1, Msn2, Msn4) that target particular osmotic stress-responsive genes [53,56]. Using chromatin immunoprecipitation (ChIP) analysis, Hog1 was shown to be a component of several distinct promoter bound complexes [53–55,58] (Fig. 2). At the *GPD1* gene promoter constitutively bound Hot1 recruits Hog1 in response to osmotic stress, while at the *STL1* promoter the binding of both Hot1 and Hog1 was demonstrated to be interdependent [53] (Fig. 2A, B). At other promoters of osmotic stress responsive genes, such as the *CTT1* and *HSP12* promoters, the zinc finger-containing transcription factors Msn2 and Msn4 recruit Hog1 following osmotic stress and the presence of Hog1 is required for the recruitment of Hot1 [53]. Surprisingly, Hot1 or Msn2–Msn4 phosphorylation by Hog1 is not essential for the regulation of Hot1-dependent and Msn2–Msn4-dependent promoters, respectively. Instead, activated Hog1 appears to mediate the recruitment of the general transcription machinery (GTM) to the promoter in response to osmotic stress through association with RNA polymerase II, subunits of mediator, and general transcription factors (GTFs) [58]. It is currently unclear whether Hog1 phosphorylates components of the GTM in addition to recruiting them.

Further evidence supporting the importance of Hog1 at osmotic stress-responsive promoters has come from studies of the Sko1 repressor which binds to subset of these promoters. In the absence of osmotic stress, Sko1 recruits the Cyc8-Tup1 co-repressor complex to repress gene transcription [54,59] (Fig. 2C). In conditions of high osmolarity, Sko1 recruits active Hog1 and is phosphorylated by Hog1 which converts the Sko1–Cyc8–Tup1 repressor complex into an activator by permitting the recruitment of the SAGA and SWI–SNF chromatin remodelling complexes [54] (Fig. 2C). Similar to Hot1- and Msn2/Msn4-dependent promoters, the active Hog1 also functions to recruit components of the GTM [54].

It is unclear whether the recruitment of Hog1 to gene promoters is required for the transcription of all Hog1-dependent genes, or just a subset of these genes. A recent genome-wide analysis involving ChIP experiments and DNA microarrays suggests the latter as Hog1 was only detected at a minority of Hog1-dependent genes [55]. This approach also

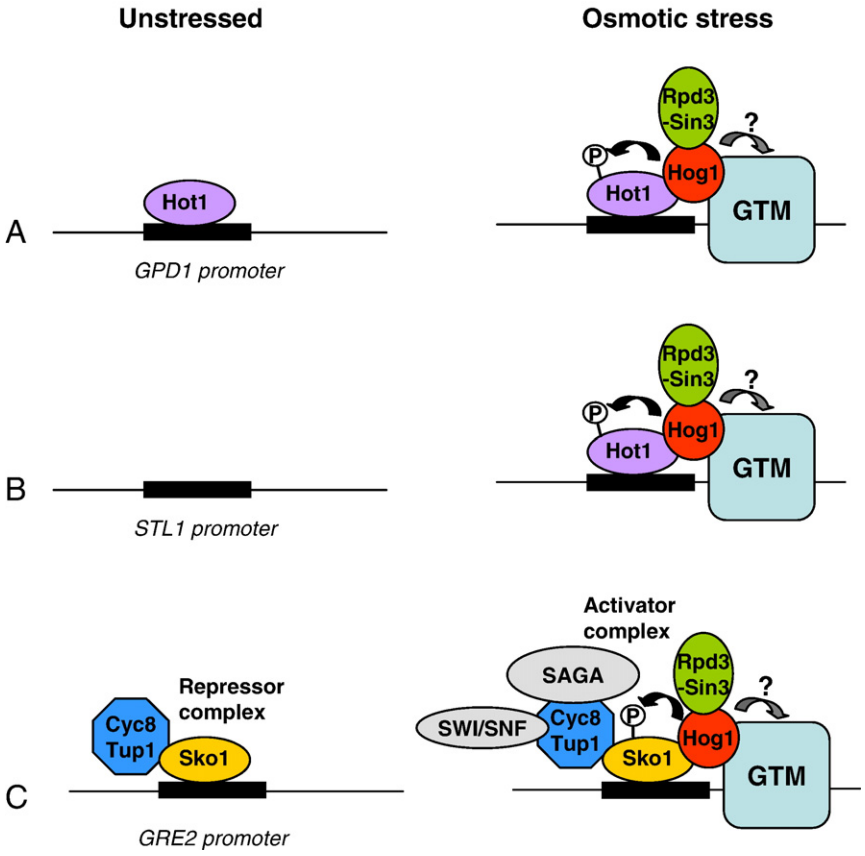

Fig. 2. The yeast Hog1 MAPK is an integral component of transcription factor complexes. In response to osmotic stress Hog1 is recruited to the promoter regions of a number of osmoresponsive genes through distinct mechanisms [53,54]. At the *GPD1* promoter (A) constitutively bound Hot1 transcription factor recruits activated Hog1 in response to osmotic stress while at the *STL1* promoter (B) osmotic stress induces the interdependent binding of Hot1 and activated Hog1. While Hog1 can phosphorylate Hot1 this does not appear to be required for transcription to occur. A third mechanism occurs at the *GRE2* promoter (C) which in unstressed cells is bound by the Sko1–Cyc8–Tup1 co-repressor complex. High osmolarity causes Sko1 to recruit activated Hog1 which phosphorylates Sko1 and converts the Sko1–Cyc8–Tup1 repressor complex to a transcriptional activator via the recruitment of the SAGA and SWI–SNF chromatin remodelling complexes. At all these promoters it is proposed that active Hog1 promotes transcription by recruiting components of the GTM including RNA polymerase II (Pol II), GTFs, subunits of mediator, as well as the Rpd3–Sin3 HDAC complex [58,123]. It is not clear whether Hog1 phosphorylation of components of the GTM also contributes to gene transcription.

revealed that other *S. cerevisiae* MAPKs are present at genes. In response to mating pheromone, the MAPKs Fus3 and Kss1 were detected at a subset of mating-specific genes [55].

Hog1, in addition to its role in the initiation of transcription, is also critical for transcriptional elongation of osmotic stress-responsive genes [60]. Active Hog1 is recruited to the coding region of these genes and enhances the association of elongating RNA polymerase II and elongation factors [55,60]. The binding of Hog1 to the transcribed regions appears to be dependent on the 3′ UTR and is independent of its role in transcriptional initiation complexes [60]. It is possible that Fus3 and Kss1 may also play a role in elongation. Indeed, both kinases show greater occupancy of the transcribed regions of the genes they associate with than the promoter regions [55]. Taken together these studies indicate a critical role for Hog1 in the initiation of transcription and in transcriptional elongation and suggest that other *S. cerevisiae* MAPKs may have similar functions.

Considering the conservation of MAPK pathways through evolution, it is highly likely that mammalian MAPKs are also components of transcriptional complexes. Indeed ERK5 may have a direct role in transcriptional activation as located within its extended C-terminus is a strong transcriptional activation domain, although the functional role of this is not understood [61]. Direct evidence of mammalian MAPK recruitment to specific gene promoters *in vivo* has been scarce, however it has recently been demonstrated using ChIP experiments that ERK1 and ERK2 are recruited to AP-1 reporter genes in a phorbol ester-dependent manner [62], while inactive JNK is recruited to the *c-jun* promoter in response to glucocorticoid [63], and p38α/β is recruited to regulatory elements located in the promoters of the muscle-specific genes *Myog* and *Ckm* [64]. In the latter example, the inhibition of p38 activity prevented the recruitment of the SWI–SNF chromatin remodelling complex and abrogated gene expression [64]. These data suggest that p38 can associate with promoter-bound complexes and selectively target SWI–SNF to distinct regulatory elements to promote the expression of muscle-specific genes. The precise mechanism by which p38 regulates these genes is unclear, however, it may involve the direct phosphorylation of the SWI–SNF complex as the BAF60 subunit can be phosphorylated by p38 *in vitro* [64].

A number of studies in mammalian cells have linked MAPK signaling to components of the GTM. p38 can bind to RNA polymerase II [58], while ERK can phosphorylate its C-terminal tail (CTD) [65]. Both p38 and ERK can phosphorylate the TATA-binding protein (TBP) component of the TFIID transcription factor complex and potentially enhance its binding to the TATA box [66,67]. p38 also enhances STAT1-dependent gene expression in response to interferon (IFN)-γ independently of its ability to phosphorylate STAT1, suggesting that p38 might be present at STAT1-regulated gene promoters and could potentially recruit and/or phosphorylate GTM components [68]. In addition to regulating RNA polymerase II-dependent transcription, ERK can regulate GTFs associated with RNA polymerases I and III including TIF-IA and TFIIIB, respectively [69,70]. Taken together these observations suggest that MAPKs may be integral components of transcriptional complexes and can regulate multiple aspects of transcriptional control at gene promoters.

3.4. MAPK scaffold proteins as part of transcriptional complexes

There is increasing evidence that MAPK pathways are regulated by scaffold proteins [15,16]. These are a diverse group of proteins that may localize MAPK components to particular cellular compartments and control their activities [15,16]. Some scaffold proteins may directly link MAPK pathways to specific substrates, including transcription factors. For example, in *Drosophila* a multi-domain protein connector of kinase to AP-1 (CKA) functions in the JNK pathway and is important for the expression of decapentaplegic (DPP) in leading edge epithelial cells [71]. CKA promotes dJNKK (Hep) activation of dJNK (Bsk) and may also link the activated JNK to its substrates by binding to the AP-1 proteins (dFos and dJun) which control *DPP* gene transcription [71].

The mammalian scaffold proteins JNK-interacting protein-1 (JIP1) and JNK-associated leucine-zipper protein (JLP) have also been reported to form complexes between JNK and p38 and some of their transcriptional targets [72,73]. In addition, JIP1 has been observed localized in the nucleus with the transcriptionally active amyloid precursor protein (APP)-intracellular domain (AICD) and the histone acetyltransferase (HAT) TIP60 [74]. The functional role of JIP1 in this complex is not known although in reporter gene assays JIP1 enhances AICD transcriptional activity [75] and displays intrinsic transcriptional activity [75,76].

It is possible that, like MAPKs, scaffold proteins may be recruited to genes. The *S. cerevisiae* scaffold protein Ste5, that coordinates and binds to the components of the mating pathway [3,16], is found occupying the same mating genes as those bound by the MAPKs Fus3 and Kss1 [55]. This suggests that scaffold proteins can coordinate the activation of MAPK pathways in the cytoplasm (or at the plasma membrane) and also regulate the action of MAPKs at their target genes within the nucleus. It will be interesting to see whether other scaffold proteins are also part of transcription factor complexes. It is reported that JIP1 can bind to the GTII regulatory element at the *GLUT2* promoter and regulate its expression [76,77] but the binding has not been confirmed *in vivo*.

4. Regulation of transcription by the interplay of MAPK pathways with other post-translational modification pathways

Transcription factors and chromatin proteins are subject to multiple post-translational modifications (PTMs) in addition to phosphorylation. These include acetylation, methylation, ubiquitination, and sumoylation amongst others. It is clear that these modifications are not occurring in isolation but can be interdependent, being either collaborative or antagonistic. In addition, the signalling pathways leading to these PTMs can cross-talk to provide a further level of regulation. Here I will focus on recent work uncovering the interplay between MAPK pathways and pathways leading to the ubiquitination, sumoylation and acetylation of transcriptional regulatory proteins.

4.1. Regulation of transcription factor ubiquitination by MAPKs

MAPKs can control the protein levels of transcription factors in cells by regulating their stability via the ubiquitin-proteosome system. Proteolysis allows for the rapid and irreversible loss of proteins and thereby enables rapid changes in cell function [78]. Ubiquitin is attached to target proteins at Lys residues by an enzyme complex consisting of E1, E2 and E3 subunits and the ubiquitinated proteins are degraded by the proteosome [78]. There are many examples of MAPKs promoting ubiquitin-dependent transcription factor degradation via phosphorylation of the factor [8]. In some cases, the transactivation of a transcription factor in response to MAPK phosphorylation is directly linked to their degradation, thereby providing a mechanism for short-lived activation. For example, the nuclear hormone receptors progesterone receptor (PR) and retinoic acid receptor-γ2 (RARγ2) are activated and subsequently degraded in response to ligand-dependent activation of the ERK and p38 signaling pathways, respectively [79,80]. Such a response may involve cooperation with other PTMs as occurs during the regulation of the haematopoietic transcription factor GATA-1. The acetylation of GATA-1 is required for its binding to DNA and its transcriptional activity [81]. Active acetylated GATA-1 is degraded following ERK phosphorylation of a number of sites in the protein [81]. Thus, only GATA-1 that is both acetylated and phosphorylated is degraded, providing a mechanism of selectively targeting the transcriptionally active GATA-1 [81].

Recent work in *S. cerevisiae* has demonstrated that the selective degradation of transcription factors can promote signaling specificity. The yeast MAPK pathways that are required for mating and filamentous growth share several common components, including the MKKK Ste11 and the MKK Ste7, but each pathway activates a distinct transcriptional program [3,82] (Fig. 3A). Genes involved in mating are regulated by the Ste12 transcription factor which binds to sites in the promoters of mating genes while genes required for filamentous growth are activated by a hetero-multimer of Ste12 and a second transcription factor, Tec1 [82]. In response to mating pheromone the MAPKs Fus3 and Kss1 are activated by the Ste11–Ste7 pathway in a complex with the scaffold protein Ste5, while during filamentous growth only Kss1 is activated by the Ste11–Ste7 pathway [82] (Fig. 3A). However, the Kss1 activated by pheromone does not up-regulate filamentous growth-specific genes except if Fus3 activity is lost, indicating that Fus3 restricts Kss1-mediated activation of these genes [82,83]. One way this occurs is by the activated Fus3 limiting the magnitude and duration of Kss1 activation, although the precise mechanism is unclear [84] (Fig. 3B). An additional mechanism involves Fus3 phosphorylating the filamentous growth-specific transcription factor Tec1 at Thr273 which leads to its ubiquitination via an SCF ubiquitin ligase complex and its degradation, thereby preventing the transcription of filamentation-specific genes [85–87] (Fig. 3B). Interestingly, the extent of Tec1 degradation is proportional to the concentration of pheromone. Therefore, at low pheromone concentrations Tec1 levels may remain high enough to allow the yeast to forage for optimal mating conditions while still being primed for mating. These studies demonstrate that the signal-induced degradation of transcription factors in competing pathways may provide an important mechanism for ensuring signaling specificity. This regulation at the level of MAPK targets allows the control of specific transcriptional outputs while providing the flexibility to permit other MAPK outputs that support the desired physiological response. In addition, as proteolysis is rapid and MAPK pathways often

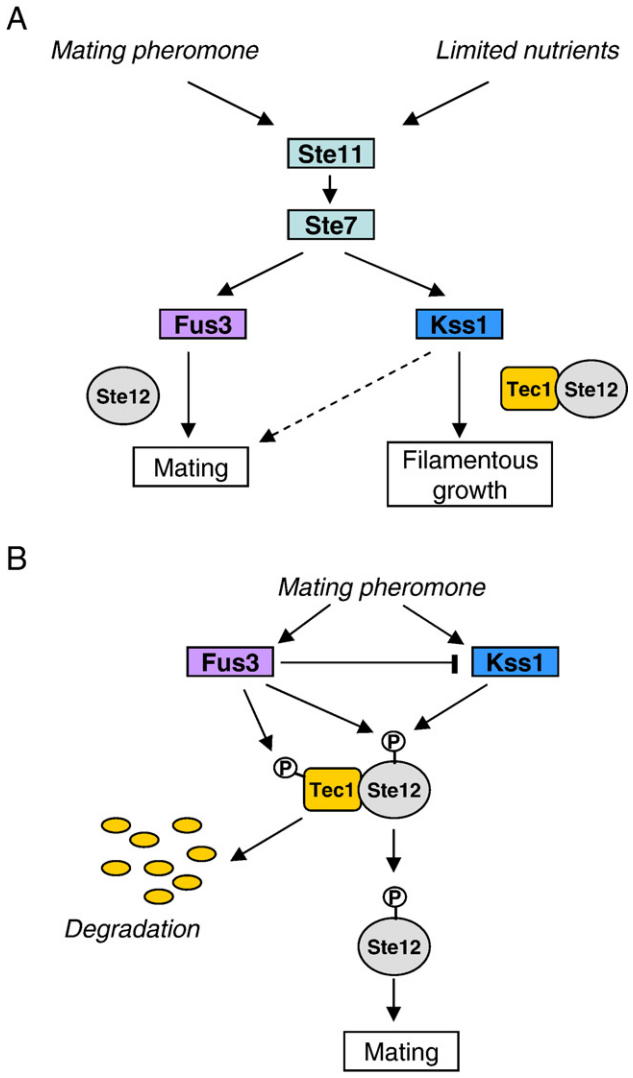

Fig. 3. The selective degradation of the Tec1 transcription factor promotes signaling specificity during yeast mating response. (A) The *S. cerevisiae* MAPK pathways that are required for mating and filamentous growth share a number of conserved components but can activate distinct transcriptional programs [3,82]. Mating genes are regulated by the transcription factor Ste12, while genes required for filamentous growth are regulated by the cooperative binding of Ste12 and Tec1 to promoters. (B) In response to pheromone both Fus3 and Kss1 MAPKs are activated leading to the activation of Ste12 by phosphorylation (P) and the transcription of mating-specific genes [82]. The activated Fus3 limits the extent and duration of Kss1 activation and also phosphorylates Tec1 at Thr273 leading to its degradation by the proteosome [83–87]. These regulatory mechanisms result in a lack of activation of genes required for filamentous growth.

share components, it allows for rapid switching between transcriptional programs.

MAPKs are also reported to promote the stability of transcription factors. As discussed in Section 3.2, the phosphorylation of c-Fos following sustained ERK1/2 activity leads to its stabilization [21,43]. However, it was recently reported that ERK5 could also regulate c-Fos stability. ERK5 phosphorylates c-Fos at sites distinct from the ERK1/2 sites and blocks c-Fos nuclear export as well as its binding to the E3 ubiquitin ligase UBR1, which can mediate c-Fos degradation [88,89] (Fig. 1B). Therefore, sustained ERK5 activity promotes c-Fos nuclear localization and stability resulting in enhanced cell growth.

It is clear that there are multiple levels of regulation of transcription factors by ubiquitination and proteolysis. For example, as mentioned previously (in Section 3.2), inactive JNK isoforms may target transcription factors including JunB, ATF-2 and p53 for degradation, although the mechanisms involved are unclear [49,90]. The role of JNK phosphorylation of c-Jun in regulating its stability is more controversial. Several studies have demonstrated that JNK phosphorylation of c-Jun stabilizes the protein and thereby contributes to its transcriptional activity [49,91], however there is also evidence that JNK phosphorylation of c-Jun can contribute to its degradation [92]. At least three distinct ubiquitin ligase complexes (Fbw7, COP1, and Itch) have been implicated as mediators of c-Jun ubiquitination and degradation [92–94]. One of these, the SCF-type ubiquitin ligase Fbw7, is reported to preferentially associate with c-Jun that has been phosphorylated by JNK and to target it for degradation [92]. The depletion of Fbw7 from neurons by siRNA resulted in increased levels of phosphorylated c-Jun, increased AP-1 activity, and increased apoptosis [92]. However, a second study found no evidence for Fbw7 recruitment to c-Jun phosphorylated at the major JNK sites (Ser63 and Ser73) but instead demonstrated that Fbw7 recruitment required the phosphorylation of the c-Jun C-terminus by glycogen synthase kinase-3 (GSK3) [95]. A possible explanation for this discrepancy is that in neurons the basal level of JNK1 activity is high and this appears to be important for regulating microtubule dynamics and neuron morphology [96,97]. However, the JNK-c-Jun pathway is a major apoptotic pathway in neurons [6,98] and Fbw7 may therefore function to dampen down the c-Jun branch of the JNK pathway that leads to apoptosis and thereby allow the neurons to tolerate potentially neurotoxic levels of JNK activity [92].

A further twist to the regulation of c-Jun is that the activity of one of the ubiquitin ligases that targets it is itself regulated by JNK phosphorylation. Itch is a HECT-domain ubiquitin ligase that targets both c-Jun and the related JunB for degradation [94]. In mice lacking either Itch or JNK1, both c-Jun and JunB accumulate in T cells and there is excessive production of Th2 cytokines such as IL-4 [99,100]. T cell activation leads to the rapid phosphorylation of Itch by JNK which increases the catalytic activity of Itch and results in increased ubiquitination and degradation of the Jun transcription factors, thereby modulating cytokine production [94]. JNK phosphorylates three sites within the Pro-rich region of Itch and disrupts an inhibitory intramolecular interaction between the WW domain and the catalytic HECT domain leading to a conformational change that enhances Itch E3 ligase activity [101]. It will be interesting to see if JNK phosphorylation of Itch regulates other Itch transcriptional targets such as SMAD2, p63, and p73 [102–104].

These recent studies on the regulation of the stability of Jun family members by the ubiquitin-proteosome system demonstrate a high degree of complexity. Several different ubiquitin ligase complexes are involved and their actions can be differentially regulated by JNK signaling. It seems likely that the protein stability of other transcriptional targets of MAPKs is regulated in a similarly complex way.

4.2. Regulation of transcription factor sumoylation by MAPKs

In recent years many transcriptional regulators have been demonstrated to be sumoylated. This involves the covalent conjugation of small ubiquitin-related modifier (SUMO) to target proteins. Analogous to ubiquitination, sumoylation occurs via a SUMO ligase complex of E1, E2 and E3 subunits [105,106]. The E1 enzyme activates SUMO which is then transferred to the target lysine residue in the substrate by the E2 conjugating enzyme Ubc9, often aided by E3 ligases including protein inhibitor of activated STAT (PIAS) proteins, RanBP2 and Pc2 [105,106]. In many substrates Ubc9 recognises the target Lys residue within a consensus sequence ψKxE (where ψ is a bulky hydrophobic residue) although additional specificity determinants have also been proposed [105–108]. Similar to phosphorylation, SUMO modification is reversible and conjugates can be targeted by SUMO isopeptidases [105,106]. The sumoylation of proteins can regulate many aspects of their function including cellular location, stability, and in the case of transcription factors, their transactivation or repressive properties [105,106].

There is evidence that the MAPK pathways can cooperate with or be antagonistic with the SUMO pathway in order to regulate transcription factor function. A prime example of this occurs as part of the regulatory crosstalk between the previously discussed mating and filamentous growth pathways in *S. cerevisiae*, where the sumoylation of the Ste12 and Tec1 transcription factors provides an additional level of regulation. In response to mating pheromone Ste12 is sumoylated dependent on Fus3 activity and this promotes Ste12 protein stability and transcriptional activity at mating genes [109]. Conversely, the filamentation pathway-specific factor Tec1 undergoes a loss of sumoylation [109] leading to its rapid degradation via the ubiquitin-proteosome pathway (as described in Section 4.1), thus contributing to a switch from the filamentous growth transcriptional program to the mating transcriptional program.

In mammalian cells sumoylation is also regulated by MAPKs. The mammalian SUMO isoform SUMO-1 is conjugated to Lys229 and Lys257 on c-Jun [110,111] but the level of sumoylation is decreased upon c-Jun phosphorylation by JNK [110]. Experiments demonstrating that the mutation of the JNK

phosphorylation sites on c-Jun leads to increased sumoylation while sumoylation-deficient mutants of c-Jun have increased transcriptional activity, indicate that sumoylation negatively regulates c-Jun activity [110,111]. A more detailed analysis of the mechanisms involved in the interplay between the SUMO and MAPK pathways has come from studies of the ETS-domain transcription factor Elk-1, which is implicated in the expression of a number of IEGs including *c-Fos*, *Egr1* and *Mcl-1* [112]. In the absence of growth promoting signals, Elk-1 activity is repressed due to SUMO conjugation to Lys residues located within a C-terminal transcriptional repression domain [113] (Fig. 4). In response to growth factor stimulation, Elk-1 is phosphorylated by ERK within its C-terminal TAD [112–114]. This leads to the activation of Elk-1 target genes by promoting the loss of SUMO conjugation and de-repression [113]. It also allows the recruitment of the Mediator complex [115] and possibly other co-activators that link Elk-1 to the GTM. One of the mechanisms by which the sumoylation of Elk-1 causes transcriptional repression is by the recruitment of a histone deacetylase-2 (HDAC2) co-repressor complex [116] (Fig. 4). This complex may remove acetyl groups from local histones and thereby promote the formation of a repressive chromatin structure. In addition to this direct role in controlling Elk-1 transcriptional activity, the sumoylation of Elk-1 is also proposed to regulate its subcellular localization by promoting its nuclear retention [117]. This suggests that sumoylation of Elk-1 may have multiple potentially coupled roles in regulating Elk-1 activity in cells.

The SUMO E3 ligases responsible for promoting the sumoylation of Elk-1 have yet to be uncovered, however a member of the PIAS family of SUMO E3 ligases does bind to Elk-1 and regulate its activity independently of its E3 ligase activity [118]. PIASxα enhances Elk-1 transcriptional activity in response to growth factors by facilitating the loss of Elk-1 sumoylation and the loss of HDAC2 complex association with Elk-1 [118] (Fig. 4). In addition, PIASxα upregulates the activity of the Elk-1 co-activator p300, which contains intrinsic HAT activity [118]. These activities of PIASxα are dependent upon Elk-1 and p300 sumoylation and require the SUMO binding domain located within PIASxα [118]. These data suggest, somewhat paradoxically, that PIAS proteins are able to promote both sumoylation and loss of sumoylation depending on the cellular context. This is supported by other recent studies that also demonstrate that PIAS proteins are multifunctional and, in addition to being SUMO E3 ligases, can have E3 ligase-independent functions including co-activation and co-repression functions [119].

Interestingly, analogous to the regulation of a ubiquitin E3 ligase by MAPK phosphorylation (as discussed in Section 4.1), PIASxα can be phosphorylated and regulated by p38 [120]. The stress-induced activation of the p38 pathway leads to an increase in Elk-1 activity mediated by p38 phosphorylation of the C-terminal TAD of Elk-1 [112]. However, only partial activation of Elk-1 occurs as p38 also phosphorylates at least two sites in PIASxα which prevents the loss of Elk-1 sumoylation and HDAC2 association, and thereby dampens down Elk-1 activity [120]. While it is not clear how p38 phosphorylation of PIASxα switches it from a co-activator of Elk-1 to a co-repressor, this represents a mechanism for graded transcriptional responses depending on the MAPK pathway activated. p38 may also regulate other aspects of PIAS function. It is reported that in response to transforming growth factor-β (TGFβ), the p38 pathway promotes the expression of PIASxβ via both increased transcription of the gene and enhanced

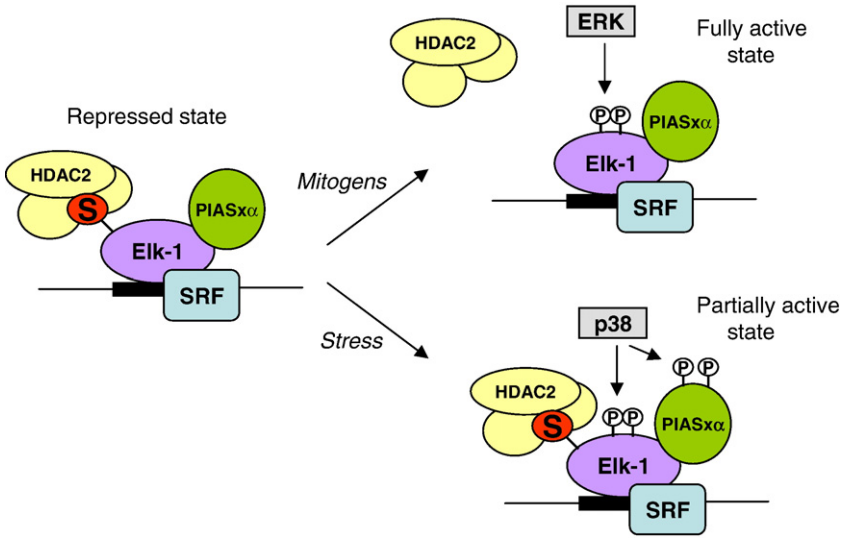

Fig. 4. Interplay between the SUMO and MAPK pathways regulates the transcription of IEGs by Elk-1. The ETS-domain transcription factor Elk-1 regulates a number of IEGs including *c-fos* and *egr-1* in response to mitogens and stress [112]. At many of these promoters Elk-1 binds as a complex with serum response factor (SRF). In unstimulated cells Elk-1 is sumoylated (S) and recruits an HDAC2 co-repressor complex [113,116]. Mitogenic stimuli cause the phosphorylation (P) of the Elk-1 C-terminal TAD leading to de-repression by the loss of both sumoylation and HDAC2 association [113,116]. This is promoted by PIASxα which acts as a co-activator of Elk-1 [118]. In response to stress, p38 MAPK phosphorylates both the transcriptional activation domain of Elk-1 and also PIASxα [120]. The phosphorylation of PIASxα by p38 prevents the loss of Elk-1 sumoylation and of the HDAC2 complex from the promoter by an unknown mechanism [120]. This results in partial Elk-1 activity and may serve to dampen down Elk-1-mediated transcription.

protein stability, which leads to increased SMAD4 sumoylation and transcriptional activity [121].

4.3. MAPK interplay with acetylation in regulating transcription

The acetylation and deacetylation of transcription factors and chromatin proteins is carried out by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively [122]. While it was originally thought that HAT's act as co-activators by promoting chromatin relaxation through histone acetylation and HDACs act as co-repressors by removing acetyl groups from histones, a more complex picture has now emerged. The functions of these factors depend on the particular promoter context and their actions can be coordinated by signaling events to temporally regulate gene expression. The previously discussed *S. cerevisiae* MAPK Hog1, which is an integral part of transcription factor complexes at osomotic stress-responsive gene promoters, is essential for the recruitment of the Rpd3–Sin3 HDAC complex to these promoters [123] (Fig. 2). This leads to the modification of local chromatin structure by histone deacetylation and increases the recruitment of RNA polymerase II and is also likely to allow the recruitment of additional co-activating factors [123].

Individual transcription factors may coordinate the actions of multiple HATs and HDACs. In response to ERK activation Elk-1 dissociates from the HDAC2 co-repressor complex (as discussed in Section 4.2) and promotes increased HAT activity of the pre-bound co-activator p300 leading to increased Elk-1 dependent gene transcription [118,124]. Elk-1 mediated gene expression can be terminated by the recruitment of an mSin3A-HDAC1 co-repressor complex to an N-terminal repression domain in the phosphorylated Elk-1 [125]. The coordinated actions of these HATs and HDACs can serve as a mechanism to allow rapid switching on and off of Elk-1-mediated transcription. A similar scenario occurs during JNK-dependent regulation of AP-1 activity during *Drosophila* metamorphosis. In this example JNK phosphorylation of the AP-1 factor dFos results in increased activity of the associated HAT Chameau (Chm) towards histone H4 residue Lys14 and promotes target gene transcription [126]. The de-phosphorylation of dFos leads to the recruitment of the HDAC dRpd3 which alters the histone modification pattern to impede gene transcription. [126]. The balance between the activities of the HAT and HDAC controls the transient activation of JNK/AP-1 target genes and establishes a link between MAPK signaling and chromatin modification in specific developmental processes [126]. It is important to note that the functional partnership between Chm and dRpd3 is specific for JNK mediated control of thoracic closure and apoptosis but does not regulate other JNK-mediated processes such as dorsal closure, where JNK coordination of the activities of other HAT and HDAC complexes may be important [126].

MAPKs can directly interact with HATs and HDACs and this can lead to changes in the activities of both the MAPKs and the HAT/HDACs. The co-activation properties of p300 and the closely related HAT CREB-binding protein (CBP) are enhanced by either ERK phosphorylation or by binding to MSK1 [127–129], while JNK phosphorylation of ATF-2 is reported to promote its instrinsic HAT activity [130], although this remains somewhat controversial. In addition, multiple mammalian MAPKs have been demonstrated to associate with HDACs. For example ERK binds to HDAC4 and may contribute to its nuclear localization [131], while HDAC3 complexes associate with JNK and the p38 isoform p38β and suppress their protein kinase activities [132,133].

In addition to regulating the activities of HATs and HDACs, MAPK signaling pathways also target histones in response to a variety of mitogenic and stress signals. For example, the histone H2A isoform, H2AX, is phosphorylated by JNK and this is required for apoptotic DNA fragmentation [134]. The site of JNK phosphorylation on H2AX, similar to only a handful of other MAPK substrates, does not conform to the minimal consensus sequence ([Ser/Thr]-Pro) [134]. This indicates that additional primary sequences containing Ser or Thr can mimic the conformation adopted by the [Ser/Thr]-Pro motif and can be recognised by MAPKs. Other histones, while not direct MAPK targets, are phosphorylated by downstream protein kinases. Histone H3 is phosphorylated at Ser10 and Ser28 by MSK1 and MSK2, downstream kinases of the ERK and p38 pathways [17,135]. This function of MSKs appears to be evolutionarily conserved as the *Drosophila* MSK homolog, JIL-1, also phosphorylates histone H3 [136]. A second protein kinase downstream of MAPK pathways, RSK2, has also been proposed as a histone H3 kinase [137] but there are conflicting reports as to its importance [138]. Interestingly, Ser28 on histone H3 can also be phosphorylated by MLTKα, a protein kinase that is related to the MKKK family of mixed-lineage kinases (MLKs) [139]. A number of past studies have proposed that histone H3 phosphorylation promotes its subsequent acetylation [138]. However, more recent experiments using cells lacking MSK1 and MSK2, where mitogen-induced histone H3 phosphorylation does not occur, demonstrate no defects in acetylation suggesting that these modifications are independent events rather than being interdependent [135,138]. This does not exclude an important role for MAPKs in regulating histone acetylation. Indeed, the JNK pathway is required for the induction of histone H4 acetylation in response to stress, although how this occurs is not clear [140]. The mechanisms by which histone phosphorylation and/or acetylation mediated by MAPK pathways control the expression of specific genes are starting to be addressed. It should be borne in mind that only a relatively small fraction of histone H3 is phosphorylated in cells and this may induce localized alterations in chromatin structure that favour the binding of specific transcription factors or promote the recruitment of chromatin remodelling complexes to mitogen- and stress-inducible genes [138,141].

5. Concluding remarks

The regulation of transcription by MAPKs is highly complex with numerous phosphorylation targets ranging from transcription factors to co-regulators to components of the GTM and chromatin proteins. MAPK signaling pathways also interact with other PTM signaling pathways at gene promoters

increasing the complexity of gene regulation. In addition, MAPK family members may play an important recruitment role at particular gene promoters. Despite the recent progress described in this review it is still a major challenge to fully understand how developmental and physiological outcomes are determined by MAPK signaling and how the multiple individual signaling events are integrated by promoter-bound transcription factor complexes and chromatin proteins.

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References

[1] C.S. Hill, R. Treisman, Transcriptional regulation by extracellular signals: mechanisms and specificity, Cell 80 (1995) 199–211.
[2] A.J. Whitmarsh, R.J. Davis, Regulation of transcription factor function by phosphorylation, Cell Mol. Life Sci. 57 (2000) 1172–1183.
[3] M.C. Gustin, J. Albertyn, M. Alexander, K. Davenport, MAP kinase pathways in the yeast *Saccharomyces cerevisiae*, Microbiol. Mol. Biol. Rev. 62 (1998) 1264–1300.
[4] L. Chang, M. Karin, Mammalian MAP kinase signaling cascades, Nature 410 (2001) 37–40.
[5] T.S. Lewis, P.S. Shapiro, N.G. Ahn, Signal transduction through MAP kinase cascades, Adv. Cancer Res. 74 (1998) 49–139.
[6] J.M. Kyriakis, J. Avruch, Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation, Physiol. Rev. 81 (2001) 807–869.
[7] X. Wang, C. Tournier, Regulation of cellular functions by the ERK5 signalling pathway, Cell Signal. 18 (2006) 753–760.
[8] S.-H. Yang, A.D. Sharrocks, A.J. Whitmarsh, Transcriptional regulation by the MAP kinase signaling cascades, Gene 320 (2003) 3–21.
[9] A.J. Whitmarsh, R.J. Davis, Transcription factor AP-1 regulation by mitogen-activated protein kinase signal transduction pathways, J. Mol. Med. 74 (1996) 589–607.
[10] C.A. Hazzalin, L.C. Mahadevan, MAPK-regulated transcription: a continuously variable gene switch? Nat. Rev. Mol. Cell. Biol. 3 (2002) 30–40.
[11] S. Gupta, T. Barrett, A.J. Whitmarsh, J. Cavanagh, H.K. Sluss, B. Derijard, R.J. Davis, Selective interaction of JNK protein kinase isoforms with transcription factors, EMBO J. 15 (1996) 2760–2770.
[12] Y. Miyata, E. Nishida, Distantly related cousins of MAP kinase: biochemical properties and possible physiological functions, Biochem. Biophys. Res. Commun. 266 (1999) 291–295.
[13] M.A. Bogoyevitch, N.W. Court, Counting on mitogen-activated protein kinases — ERKs 3, 4, 5, 6, 7 and 8, Cell. Signal. 16 (2004) 1345–1354.
[14] S.M. Keyse, Protein phosphatases and the regulation of mitogen-activated protein kinase signaling, Curr. Opin. Cell Biol. 12 (2000) 186–192.
[15] D.K. Morrison, R.J. Davis, Regulation of MAP kinase signaling modules by scaffold proteins in mammals, Annu. Rev. Cell Dev. Biol. 19 (2003) 91–118.
[16] N. Dard, M. Peter, Scaffold proteins in MAP kinase signaling: more than simple passive activating platforms, Bioessays 28 (2006) 146–156.
[17] P.P. Roux, J. Blenis, ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions, Microbiol. Mol. Biol. Rev. 68 (2004) 320–344.
[18] Z. Galcheva-Gargova, B. Derijard, I.H. Wu, R.J. Davis, An osmosensing signal transduction pathway in mammalian cells, Science 265 (1994) 806–808.
[19] A.D. Sharrocks, S.-H. Yang, A. Galanis, Docking domains and substrate-specificity determination for MAP kinases, Trends Biochem. Sci. 25 (2000) 448–453.
[20] T. Tanoue, E. Nishida, Molecular recognitions in the MAP kinase cascades, Cell Signal. 15 (2003) 455–462.
[21] L.O. Murphy, J. Blenis, MAPK signal specificity: the right place at the right time, Trends Biochem. Sci. 31 (2006) 268–275.
[22] J.W. Edmunds, L.C. Mahadevan, MAP kinases as structural adaptors and enzymatic activators in transcription complexes, J. Cell. Sci. 117 (2004) 3715–3723.
[23] C.I. Chang, B.E. Xu, R. Akella, M.H. Cobb, E.J. Goldsmith, Crystal structures of MAP kinase p38 complexed to the docking sites on its nuclear substrate MEF2A and activator MKK3b, Mol. Cell 9 (2002) 1241–1249.
[24] T. Zhou, L. Sun, J. Humphreys, E.J. Goldsmith, Docking interactions induce exposure of activation loop in the MAP kinase ERK2, Structure 14 (2006) 1011–1019.
[25] A. Remenyi, M.C. Good, R.P. Bhattacharyya, W.A. Lim, The role of docking interactions in mediating signaling input, output, and discrimination in the yeast MAPK network, Mol. Cell 20 (2005) 951–962.
[26] D. Jacobs, D. Glossip, H. Xing, A.J. Muslin, K. Kornfeld, Multiple docking sites on substrate proteins form a modular system that mediates recognition by ERK MAP kinase, Genes Dev. 13 (1999) 163–175.
[27] A. Galanis, S.-H. Yang, A.D. Sharrocks, Selective targeting of MAPKs to the ETS domain transcription factor SAP-1, J. Biol. Chem. 276 (2001) 965–973.
[28] J.J. Seidel, B.J. Graves, An ERK2 docking site in the pointed domain distinguishes a subset of ETS transcription factors, Genes Dev. 16 (2002) 127–137.
[29] D.M. Molina, S. Grewal, L. Bardwell, Characterization of an ERK-binding domain in microphthalmia-associated transcription factor and differential inhibition of ERK2-mediated substrate phosphorylation, J. Biol. Chem. 280 (2005) 42051–42060.
[30] M. Vinciguerra, A. Vivacqua, G. Fasanella, A. Gallo, C. Cuozzo, A. Morano, M. Maggiolini, A.M. Musti, Differential phosphorylation of c-Jun and JunD in response to the epidermal growth factor is determined by the structure of MAPK targeting sequences, J. Biol. Chem. 279 (2004) 9634–9641.
[31] T. Kallunki, T. Deng, M. Hibi, M. Karin, c-Jun can recruit JNK to phosphorylate dimerization partners via specific docking interactions, Cell 87 (1996) 929–939.
[32] D.A. Fantz, D. Jacobs, D. Glossip, K. Kornfeld, Docking sites on substrate proteins direct extracellular signal-regulated kinase to phosphorylate specific residues, J. Biol. Chem. 276 (2001) 27256–27265.
[33] C. Ducret, S.M. Maira, Y. Lutz, B. Wasylyk, The ternary complex factor Net contains two distinct elements that mediate different responses to MAP kinase signalling cascades, Oncogene 19 (2000) 5063–5072.
[34] J.M. English, M.H. Cobb, Pharmacological inhibitors of MAPK pathways, Trends Pharmacol. Sci. 23 (2002) 40–45.
[35] M.A. Bogoyevitch, Therapeutic promise of JNK ATP-noncompetitive inhibitors, Trends Mol. Med. 11 (2005) 232–239.
[36] C.N. Hancock, A. Macias, E.K. Lee, S.Y. Yu, A.D. Mackerell Jr., P. Shapiro, Identification of novel extracellular signal-regulated kinase docking domain inhibitors, J. Med. Chem. 48 (2005) 4586–4595.
[37] T. Lee, A.N. Hoofnagle, Y. Kabuyama, J. Stroud, X. Min, E.J. Goldsmith, L. Chen, K.A. Resing, N.G. Ahn, Docking motif interactions in MAP kinases revealed by hydrogen exchange mass spectrometry, Mol. Cell 14 (2004) 43–55.
[38] C.A. Dimitri, W. Dowdle, J.P. MacKeigan, J. Blenis, L.O. Murphy, Spatially separate docking sites on ERK2 regulate distinct signaling events in vivo, Curr. Biol. 15 (2005) 1319–1324.
[39] F. Qiao, B. Harada, H. Song, J. Whitelegge, A.J. Courey, J.U. Bowie, Mae inhibits pointed-P2 transcriptional activity by blocking its MAPK docking site, EMBO J. 25 (2006) 70–79.
[40] C.J. Marshall, Specificity of receptor tyrosine kinase signaling: transient versus sustained extracellular signal-regulated kinase activation, Cell 80 (1995) 179–185.
[41] T. Yamamoto, M. Ebisuya, F. Ashida, K. Okamoto, S. Yonehara, E.

Nishida, Continuous ERK activation downregulates antiproliferative genes throughout G1 phase to allow cell-cycle progression, Curr. Biol. 16 (2006) 1171–1182.
[42] J. Hess, P. Angel, M. Schorpp-Kistner, AP-1 subunits: quarrel and harmony among siblings, J. Cell. Sci. 117 (2004) 5965–5973.
[43] L.O. Murphy, S. Smith, R.H. Chen, D.C. Fingar, J. Blenis, Molecular interpretation of ERK signal duration by immediate early gene products, Nat. Cell Biol. 4 (2002) 556–564.
[44] L.O. Murphy, J.P. MacKeigan, J. Blenis, A network of immediate early gene products propagates subtle differences in mitogen-activated protein kinase signal amplitude and duration, Mol. Cell Biol. 24 (2004) 144–153.
[45] J.J. Ventura, A. Hubner, C. Zhang, R.A. Flavell, K.M. Shokat, R.J. Davis, Chemical genetic analysis of the time course of signal transduction by JNK, Mol. Cell 21 (2006) 701–710.
[46] N. Chen, Q.-B. She, A.M. Bode, Z. Dong, Differential gene expression profiles of Jnk1- and Jnk2-deficient murine fibroblast cells, Cancer Res. 62 (2002) 1300–1304.
[47] C. Tournier, P. Hess, D.D. Yang, J. Xu, T.K. Turner, A. Nimmual, D. Bar-Sagi, S.N. Jones, R.A. Flavell, R.J. Davis, Requirement of JNK for stress-induced activation of the cytochrome *c*-mediated death pathway, Science 288 (2000) 870–874.
[48] K. Sabapathy, K. Hochedlinger, S.Y. Nam, A. Bauer, M. Karin, E.F. Wagner, Distinct roles for JNK1 and JNK2 in regulating JNK activity and c-Jun-dependent cell proliferation, Mol. Cell 15 (2004) 713–725.
[49] S.Y. Fuchs, B. Xie, V. Adler, V.A. Fried, R.J. Davis, Z. Ronai, c-Jun NH2-terminal kinases target the ubiquitination of their associated transcription factors, J. Biol. Chem. 272 (1997) 32163–32168.
[50] A. Jaeschke, M. Karasarides, J.J. Ventura, A. Ehrhardt, C. Zhang, R.A. Flavell, K.M. Shokat, R.J. Davis, JNK2 is a positive regulator of the c-Jun transcription factor, Mol. Cell 23 (2006) 899–911.
[51] T. Kallunki, B. Su, I. Tsigelny, H.K. Sluss, B. Derijard, G. Moore, R.J. Davis, M. Karin, JNK2 contains a specificity determining region responsible for efficient c-Jun binding and phosphorylation, Genes Dev. 8 (1994) 2996–3007.
[52] S. Polychronopoulos, M. Verykokakis, M.N. Yazicioglu, M. Sakarellos-Daitsiotis, M.H. Cobb, G. Mavrothalassitis, The transcriptional ETS2 repressor factor associates with active and inactive Erks through distinct FXF motifs, J. Biol. Chem. 281 (2006) 25601–25611.
[53] P.M. Alepuz, A. Jovanovic, V. Reiser, G. Ammerer, Stress-induced map kinase Hog1 is part of transcription activation complexes, Mol. Cell 7 (2001) 767–777.
[54] M. Proft, K. Struhl, Hog1 kinase converts the Sko1–Cyc8–Tup1 repressor complex into an activator that recruits SAGA and SWI/SNF in response to osmotic stress, Mol. Cell 9 (2002) 1307–1317.
[55] D.K. Pokholok, J. Zeitlinger, N.M. Hannett, D.B. Reynolds, R.A. Young, Activated signal transduction kinases frequently occupy target genes, Science 313 (2006) 533–536.
[56] P.J. Westfall, D.R. Ballon, J. Thorner, When the stress of your environment makes you go HOG wild, Science 306 (2004) 1511–1512.
[57] M. Proft, K. Struhl, MAP kinase-mediated stress relief that precedes and regulates the timing of transcriptional induction, Cell 118 (2004) 351–361.
[58] P.M. Alepuz, E. de Nadal, M. Zapater, G. Ammerer, F. Posas, Osmostress-induced transcription by Hot1 depends on a Hog1-mediated recruitment of the RNA Pol II, EMBO J. 22 (2003) 2433–2442.
[59] M. Proft, A. Pascual-Ahuir, E. de Nadal, J. Arino, R. Serrano, F. Posas, Regulation of the Sko1 transcriptional repressor by the Hog1 MAP kinase in response to osmotic stress, EMBO J. 20 (2001) 1123–1133.
[60] M. Proft, G. Mas, E. de Nadal, A. Vendrell, N. Noriega, K. Struhl, F. Posas, The stress-activated Hog1 kinase is a selective transcriptional elongation factor for genes responding to osmotic stress, Mol. Cell 23 (2006) 241–250.
[61] H.G. Kasler, J. Victoria, O. Duramad, A. Winoto, ERK5 is a novel type of mitogen-activated protein kinase containing a transcriptional activation domain, Mol. Cell Biol. 20 (2000) 8382–8389.
[62] M. Benkoussa, C. Brand, M.H. Delmotte, P. Formstecher, P. Lefebvre, Retinoic acid receptors inhibit AP-1 activation by regulating extracellular signal-regulated kinase and CBP recruitment to an AP1-responsive promoter, Mol. Cell Biol. 22 (2002) 4522–4534.
[63] A. Bruna, M. Nicolas, A. Munoz, J.M. Kyriakis, C. Caelles, Glucocorticoid receptor-JNK interaction mediates inhibition of the JNK pathway by glucocorticoids, EMBO J. 22 (2003) 6035–6044.
[64] C. Simone, S.V. Forcales, D.A. Hill, A.N. Imbalzano, L. Latella, P.L. Puri, p38 pathway targets SWI–SNF chromatin-remodeling complex to muscle-specific loci, Nat. Genet. 36 (2004) 738–743.
[65] T. Oelgeschlager, Regulation of RNA polymerase II activity by CTD phosphorylation and cell cycle control, J. Cell Physiol. 190 (2002) 160–169.
[66] A.B. Carter, K.L. Knudtson, M.M. Monick, G.W. Hunninghake, The p38 mitogen-activated protein kinase is required for NF-kappaB-dependent gene expression. The role of TATA-binding protein (TBP), J. Biol. Chem. 274 (1999) 30858–30863.
[67] J.R. Biggs, N.G. Ahn, A.S. Kraft, Activation of the mitogen-activated protein kinase pathway in U937 leukemic cells induces phosphorylation of the amino terminus of the TATA-binding protein, Cell Growth Diff. 9 (1998) 667–676.
[68] K. Ramsauer, I. Sadzak, A. Porras, A. Pilz, A.R. Nebreda, T. Decker, P. Kovarik, p38 MAPK enhances STAT1-dependent transcription independently of Ser-727 phosphorylation, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 12859–12864.
[69] J. Zhao, X. Yuan, M. Frodin, I. Grummt, ERK-dependent phosphorylation of the transcription initiation factor TIF-IA is required for RNA polymerase I transcription and cell growth, Mol. Cell 11 (2003) 405–413.
[70] Z.A. Felton-Edkins, J.A. Fairley, E.L. Graham, I.M. Johnston, R.J. White, P.H. Scott, The mitogen-activated protein (MAP) kinase ERK induces tRNA synthesis by phosphorylating TFIIIB, EMBO J. 22 (2003) 2422–2432.
[71] H.-W. Chen, M.J. Marinissen, S.-W. Oh, X. Chen, M. Melnick, N. Perrimon, J.S. Gutkind, S.X. Hou, CKA, a novel multidomain protein, regulates the JUN N-terminal kinase signal transduction pathway in *Drosophila*, Mol. Cell Biol. 22 (2002) 1792–1803.
[72] Y. Cai, M.S. Lechner, D. Nihalani, M.J. Prindle, L.B. Holzman, G.R. Dressler, Phosphorylation of Pax2 by the c-Jun N-terminal kinase and enhanced Pax2-dependent transcriptional activation, J. Biol. Chem. 277 (2002) 1217–1222.
[73] C.M. Lee, D. Onesime, C.D. Reddy, N. Dhanasekaran, E.P. Reddy, JLP: A scaffolding protein that tethers JNK/p38MAPK signaling modules and transcription factors, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 14189–14194.
[74] R.C. von Rotz, B.M. Kohli, J. Bosset, M. Meier, T. Suzuki, R.M. Nitsch, U. Konietzko, The APP intracellular domain forms nuclear multiprotein complexes and regulates the transcription of its own precursor, J. Cell Sci. 117 (2004) 4435–4448.
[75] M.H. Scheinfeld, S. Matsuda, L. D'Adamio, JNK-interacting protein-1 promotes transcription of Aβ protein precursor but not Aβ precursor-like proteins, mechanistically different than Fe65, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 1729–1734.
[76] C. Bonny, P. Nicod, G. Waeber, IB1, a JIP1-related nuclear protein present in insulin-secreting cells, J. Biol. Chem. 273 (1998) 1843–1846.
[77] G. Waeber, J. Delplanque, C. Bonny, V. Mooser, M. Steinmann, C. Widmann, A. Maillard, J. Miklossy, C. Dina, E.H. Hani, N. Vionnet, P. Nicod, P. Boutin, P. Froguel, The gene MAPK8IP1, encoding islet-brain-1, is a candidate for type 2 diabetes, Nat. Genet. 24 (2000) 291–295.
[78] M.H. Glickman, A. Ciechanover, The ubiquitin-proteosome proteolytic pathway: destruction for the sake of construction, Physiol. Rev. 82 (2002) 373–428.
[79] T. Shen, K.B. Horwitz, C.A. Lange, Transcriptional hyperactivity of human progesterone receptors is coupled to their ligand-dependent down-regulation by mitogen-activated protein kinase-dependent phosphorylation of serine 294, Mol. Cell Biol. 21 (2001) 6122–6131.
[80] M. Gianni, A. Bauer, E. Garattini, P. Chambon, C. Rochette-Egly, Phosphorylation by p38MAPK and recruitment of SUG-1 are required for RA-induced RAR gamma degradation and transactivation, EMBO J. 21 (2002) 3760–3769.
[81] A. Hernandez-Hernandez, P. Ray, G. Litos, M. Ciro, S. Ottolenghi, H. Beug, J. Boyes, Acetylation and MAPK phosphorylation cooperate to

regulate the degradation of active GATA-1, EMBO J. 25 (2006) 3254–3274.
[82] M.A. Schwartz, H.D. Madhani, Principles of MAP kinase signaling specificity in *Saccharomyces cerevisiae*, Annu. Rev. Genet. 38 (2004) 725–748.
[83] E.A. Elion, M. Qi, W. Chen, Signaling specificity in yeast, Science 307 (2005) 687–688.
[84] W. Sabbagh Jr., L.J. Flatauer, A.J. Bardwell, L. Bardwell, Specificity of MAP kinase signaling in yeast differentiation involves transient versus sustained MAPK activation, Mol. Cell 8 (2001) 683–691.
[85] M.Z. Bao, M.A. Schwartz, G.T. Cantin, J.R. Yates III, H.D. Madhani, Pheromone-dependent destruction of the Tec1 transcription factor is required for MAP kinase signaling specificity in yeast, Cell 119 (2004) 991–1000.
[86] S. Chou, L. Huang, H. Liu, Fus3-regulated Tec1 degradation through SCFcdc4 determines MAPK signaling specificity during mating in yeast, Cell 119 (2004) 981–990.
[87] S. Bruckner, T. Kohler, G.H. Braus, B. Heise, M. Bolte, H.U. Mosch, Differential regulation of Tec1 by Fus3 and Kss1 confers signaling specificity in yeast development, Curr. Genet. 46 (2004) 331–342.
[88] K. Terasawa, K. Okazaki, E. Nishida, Regulation of c-Fos and Fra-1 by the MEK5-ERK5 pathway, Genes Cells 8 (2003) 263–273.
[89] T. Sasaki, H. Kojima, R. Kishimoto, A. Ikeda, H. Kunimoto, K. Nakajima, Spatiotemporal regulation of c-Fos by ERK5 and the E3 ubiquitin ligase UBR1, and its biological role, Mol. Cell 24 (2006) 63–75.
[90] S.Y. Fuchs, V. Adler, T. Buschmann, Z. Yin, X. Wu, S.N. Jones, Z. Ronai, JNK targets p53 ubiquitination and degradation in non-stressed cells, Genes Dev. 12 (1998) 2658–2663.
[91] A.M. Musti, M. Treier, D. Bohmann, Reduced ubiquitin-dependent degradation of c-Jun after phosphorylation by MAP kinases, Science 275 (1997) 400–402.
[92] A.S. Nateri, L. Riera-Sans, C. Da Costa, A. Behrens, The ubiquitin ligase SCF Fbw7 antagonizes apoptotic JNK signaling, Science 303 (2004) 1374–1378.
[93] I.E. Wertz, K.M. O'Rourke, Z. Zhang, D. Doman, D. Arnott, R.J. Deshaies, V.M. Dixit, Human de-etiolated-1 regulates c-Jun by assembling a CUL4A ubiquitin ligase, Science 303 (2004) 1371–1374.
[94] M. Gao, T. Labuda, Y. Xia, E. Gallagher, D. Fang, Y.C. Liu, M. Karin, Jun turnover is controlled through JNK-dependent phosphorylation of the E3 ligase Itch, Science 306 (2004) 271–275.
[95] W. Wei, J. Jin, S. Schlisio, J.W. Harper, W.G. Kaelin Jr., The v-Jun point mutation allows c-Jun to escape GSK3-dependent recognition and destruction by the Fbw7 ubiquitin ligase, Cancer Cell 8 (2005) 25–33.
[96] L. Chang, Y. Jones, M.H. Ellisman, L.S. Goldstein, M. Karin, JNK1 is required for maintenance of neuronal microtubules and controls phosphorylation of microtubule-associated proteins, Dev. Cell 4 (2003) 521–533.
[97] B. Bjorkblom, N. Ostman, V. Hongisto, V. Komarovski, J.J. Filen, T.A. Nyman, T. Kallunki, M.J. Courtney, E.T. Coffey, Constitutively active cytoplasmic c-Jun N-terminal kinase 1 is a dominant regulator of dendritic architecture: role of microtubule-associated protein 2 as an effector, J. Neurosci. 25 (2005) 6350–6361.
[98] S.J. Harper, P. LoGrasso, Signaling for survival and death in neurons: the role of stress-activated kinases, JNK and p38, Cell Signal. 13 (2001) 299–310.
[99] D. Fang, C. Elly, B. Gao, N. Fang, Y. Altman, C. Joazeiro, T. Hunter, N. Copeland, N. Jenkins, Y.C. Liu, Dysregulation of T lymphocyte function in itchy mice: a role for Itch in TH2 differentiation, Nat. Immunol. 3 (2002) 281–287.
[100] C. Dong, D.D. Yang, M. Wysk, A.J. Whitmarsh, R.J. Davis, R.A. Flavell, Defective T cell differentiation in the absence of Jnk1, Science 282 (1998) 2092–2095.
[101] E. Gallagher, M. Gao, Y.-C. Liu, M. Karin, Activation of the E3 ubiquitin ligase Itch through a phosphorylation-induced conformational change, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 1717–1722.
[102] Y. Bai, C. Yang, K. Hu, Y.C. Liu, Itch E3 ligase-mediated regulation of TGF-beta signaling by modulating Smad2 phosphorylation, Mol. Cell 15 (2004) 825–831.
[103] M. Rossi, R.I. Aqeilan, M. Neale, E. Candi, P. Salomoni, R.A. Knight, C.M. Croce, G. Melino, The E3 ubiquitin ligase Itch controls the protein stability of p63, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 12753–12758.
[104] M. Rossi, V. De Laurenzi, E. Munarriz, D.R. Green, Y.C. Liu, K.H. Vousden, G. Cesareni, G. Melino, The ubiquitin-protein ligase Itch regulates p73 stability, EMBO J. 24 (2005) 836–848.
[105] R.T. Hay, SUMO: a history of modification, Mol. Cell 18 (2005) 1–12.
[106] R.S. Hilgarth, L.A. Murphy, H.S. Skaggs, D.C. Wilkerson, H. Xing, K.D. Sarge, Regulation and function of SUMO modification, J. Biol. Chem. 279 (2004) 53899–53902.
[107] V. Hietakangas, J. Anckar, H.A. Blomster, M. Fujimoto, J.J. Palvimo, A. Nakai, L. Sistonen, PDSM, a motif for phosphorylation-dependent SUMO modification, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 45–50.
[108] S.-H. Yang, A. Galanis, J. Witty, A.D. Sharrocks, An extended consensus motif enhances the specificity of substrate modification by SUMO, EMBO J. 25 (2006) 5083–5093.
[109] Y. Wang, H.G. Dohlman, Pheromone-regulated sumoylation of transcription factors that mediate the invasive to mating developmental switch in yeast, J. Biol. Chem. 281 (2006) 1964–1969.
[110] S. Muller, M. Berger, F. Lehembre, J.-S. Seeler, Y. Haupt, A. Dejean, c-Jun and p53 activity is modulated by SUMO-1 modification, J. Biol. Chem. 275 (2000) 13321–13329.
[111] G. Bossis, C.E. Malnou, R. Farras, E. Andermarcher, R. Hipskind, M. Rodriguez, D. Schmidt, S. Muller, I. Jariel-Encontre, M. Piechaczyk, Down-regulation of c-Fos/c-Jun AP-1 dimer activity by sumoylation, Mol. Cell Biol. 25 (2005) 6964–6979.
[112] P.E. Shaw, J. Saxton, Ternary complex factors: prime nuclear targets for mitogen-activated protein kinases, Int. J. Biochem. Cell Biol. 35 (2003) 1210–1226.
[113] S.-H. Yang, E. Jaffray, R.T. Hay, A.D. Sharrocks, Dynamic interplay of the SUMO and ERK pathways in regulating Elk-1 transcriptional activity, Mol. Cell 12 (2003) 63–74.
[114] R. Marais, J. Wynne, R. Treisman, The SRF accessory protein Elk-1 contains a growth factor-regulated transcriptional activation domain, Cell 73 (1993) 381–393.
[115] J.L. Stevens, G.T. Cantin, G. Wang, A. Shevchenko, A. Shevchenko, A.J. Berk, Transcription control by E1A and MAP kinase pathway via Sur2 mediator subunit, Science 296 (2002) 755–758.
[116] S.-H. Yang, A.D. Sharrocks, SUMO promotes HDAC-mediated transcriptional repression, Mol. Cell 13 (2004) 611–617.
[117] S. Salinas, A. Briancon-Marjollet, G. Bossis, M.A. Lopez, M. Piechaczyk, I. Jarial-Encontre, A. Debant, R.A. Hipskind, SUMOylation regulates nucleo-cytoplasmic shuttling of Elk-1, J. Cell Biol. 165 (2004) 767–773.
[118] S.-H. Yang, A.D. Sharrocks, PIASx acts as an Elk-1 coactivator by facilitating derepression, EMBO J. 24 (2005) 2161–2171.
[119] A.D. Sharrocks, PIAS proteins and transcriptional regulation — more than just SUMO E3 ligases? Genes Dev. 20 (2006) 754–758.
[120] S.-H. Yang, A.D. Sharrocks, PIASxα differentially regulates the amplitudes of transcriptional responses following activation of the ERK and p38 MAPK pathways, Mol. Cell 22 (2006) 477–487.
[121] T. Ohshima, K. Shimotohno, Transforming growth factor-beta-mediated signaling via the p38 MAP kinase pathway activates Smad-dependent transcription through SUMO-1 modification of Smad4, J. Biol. Chem. 278 (2003) 50833–50842.
[122] M.H. Kuo, C.D. Allis, Roles of acetyltransferases and deacetylases in gene regulation, Bioessays 20 (1998) 615–626.
[123] E. de Nadal, M. Zapater, P.M. Alepuz, L. Sumoy, G. Mas, F. Posas, The MAPK Hog1 recruits Rpd3 histone deacetylase to activate osmoresponsive genes, Nature 427 (2004) 370–374.
[124] Q.J. Li, S.-H. Yang, Y. Maeda, F.M. Sladek, A.D. Sharrocks, M. Martins-Green, MAP kinase phosphorylation-dependent activation of Elk-1 leads to activation of the co-activator p300, EMBO J. 22 (2003) 281–291.
[125] S.-H. Yang, E. Vickers, A. Brehm, T. Kouzarides, A.D. Sharrocks, Temporal recruitment of the mSin3A-histone deacetylase corepressor complex to the ETS domain transcription factor Elk-1, Mol. Cell Biol. 21 (2001) 2802–2814.

[126] B. Miotto, T. Sagnier, H. Berenger, D. Bohmann, J. Pradel, Y. Graba, Chameau HAT and DRpd3 HDAC function as antagonistic cofactors of JNK/AP-1-dependent transcription during *Drosophila* metamorphosis, Genes Dev. 20 (2006) 101–112.

[127] Y.Z. Liu, N.S. Thomas, D.S. Latchman, CBP associates with the p42/p44 MAPK enzymes and is phosphorylated following NGF treatment, Neuroreport 10 (1999) 1239–1243.

[128] R. Gusterson, B. Brar, D. Faulkes, A. Giordano, J. Chrivia, D.S. Latchman, The transcriptional co-activators CBP and p300 are activated via phenylephrine through the p42/p44 MAPK cascade, J. Biol. Chem. 277 (2002) 2517–2524.

[129] R. Janknecht, Regulation of the ER81 transcription factor and its coactivators by mitogen- and stress-activated protein kinase (MSK1), Oncogene 22 (2003) 746–755.

[130] H. Kawasaki, L. Schiltz, R. Chiu, K. Itakura, K. Taira, Y. Nakatani, K.K. Yokoyama, ATF-2 has intrinsic acetyltransferase activity which is modulated by phosphorylation, Nature 405 (2000) 195–200.

[131] X. Zhou, V.M. Richon, A.H. Wang, X.J. Yang, R.A. Rifkind, P.A. Marks, Histone deacetylase 4 associates with extracellular signal-regulated kinases 1 and 2, and its cellular localization is regulated by oncogenic Ras, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 14329–14333.

[132] J. Zhang, M. Kalkum, B.T. Chait, R.G. Roeder, The N-CoR-HDAC3 nuclear receptor corepressor complex inhibits the JNK pathway through the integral subunit GPS2, Mol. Cell 9 (2002) 611–623.

[133] U. Mahlknecht, J. Will, A. Varin, D. Hoelzer, G. Herbein, Histone deacetylase 3, a class I histone deacetylase, suppresses MAPK11-mediated activating transcription factor-2 activation and represses TNF gene expression, J. Immunol. 173 (2004) 3979–3990.

[134] C. Lu, F. Zhu, Y.Y. Cho, F. Tang, T. Zykova, W.-Y. Ma, A.M. Bode, Z. Dong, Cell apoptosis: requirement of H2AX in DNA ladder formation, but not for the activation of caspase-3, Mol. Cell 23 (2006) 121–132.

[135] A. Soloaga, S. Thomson, G.R. Wiggin, N. Rampersaud, M.H. Dyson, C.A. Hazzalin, L.C. Mahadevan, J.S. Arthur, MSK2 and MSK1 mediate the mitogen- and stress-induced phosphorylation of histone H3 and HMG-14, EMBO J. 22 (2003) 2788–2797.

[136] Y. Wang, W. Zhang, Y. Jin, J. Johansen, K.M. Johansen, The JIL-1 tandem kinase mediates histone H3 phosphorylation and is required for maintenance of chromatin structure in *Drosophila*, Cell 105 (2001) 433–443.

[137] P. Sassone-Corsi, C.A. Mizzen, P. Cheung, C. Crosio, L. Monaco, S. Jacquot, A. Hanauer, C.D. Allis, Requirement of Rsk2 for epidermal growth factor-activated phosphorylation of histone H3, Science 285 (1999) 886–891.

[138] A.L. Clayton, L.C. Mahadevan, MAP kinase-mediated phosphorylation of histone H3 and inducible gene regulation, FEBS Lett. 546 (2003) 51–58.

[139] H.S. Choi, B.Y. Choi, Y.Y. Cho, F. Zhu, A.M. Bode, Z. Dong, Phosphorylation of Ser28 in histone H3 by mixed lineage kinase-like mitogen-activated protein triple kinase alpha, J. Biol. Chem. 280 (2005) 13545–13553.

[140] A.S. Alberts, O. Geneste, R. Treisman, Activation of SRF-regulated chromosomal templates by Rho-family GTPases requires a signal that also induces H4 hyperacetylation, Cell 92 (1998) 475–487.

[141] S. Saccani, S. Pantano, G. Natoli, p38-dependent marking of inflammatory genes for increased NF-κB recruitment, Nat. Immunol. 3 (2002) 69–75.